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The Safety of Military Immunization and the Risk of Insulin-Dependent Diabetes

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ABSTRACT: Vaccines have been linked to the development of autoimmune type I (insulin dependent) diabetes (IDDM) in children. Through a literature review of published data on the incidence of IDDM in adults, this article attempts to determine whether vaccination of adults in the military is associated with an increased risk of IDDM. The authors identified published data on the incidence of IDDM in white US sailors, conscripted European men, and nonconscripted European women from 5 countries. Data indicated that in European countries where only men are drafted, men have 1.7 times (range: 1.53-1.84) the risk of developing IDDM as women. In the US Navy, where men and women receive military vaccines, the incidence of IDDM is less common in men (relative risk 0.8; range 0.64-0.97). Diabetes is also more common in highly immunized US military men than in less-immunized conscripted European men (1.6; 1.45-1.73). The risk of IDDM is even more pronounced in US Navy women compared to nonconscripted European women (3.4; 2.7-4.26). The incidence of IDDM increases with time in heavily immunized US Navy men and women. Incidence of IDDM in US women sailors increases from 12.6 to 33.2 cases/100,000 between the ages of 17 and 19 and between 30 and 34 (relative risk 2.63; 1.04-6.69). By contrast, the incidence of IDDM declines in nonconscripted European women, from 10.6/100,000 in women between the ages of 15 and 19 to 5.9 cases/100,000 in women from 30 to 34 (relative risk 0.56; 0.44-0.72). The authors conclude that exposure to military immunization is strongly associated with an increased risk of IDDM.

Introduction

American troops are heavily immunized, and this policy has drawn criticism. Military personnel are forced to receive vaccines for which no long-term controlled safety studies have been performed.[1,2] Recently, military physicians have reported that the anthrax vaccine is safe.[3] By contrast, we have found consistent data that numerous vaccines have been associated with an increased risk of insulin-dependent diabetes (IDDM),[4-6] an autoimmune disease. We attempted to determine if immunization of military personnel is associated with an increased risk of IDDM.

Methods

Medline was searched to locate publications on the incidence of IDDM in civilians aged 18 to 35 and people in the military in western industrialized nations. Key words used in the Medline search were *diabetes, insulin,* and *incidence*. We used the reference lists in the papers we found to find additional texts. We had planned prospectively to include only papers on white populations from Western European countries, the United States, Canada, Australia, and New Zealand because we felt the standards of living and medical care in white populations in these countries were similar and because our previous studies had revealed an association between immunization and diabetes in children of all colors living in these countries. We limited our search to papers containing incidence data primarily from 1975 to the present and containing at least 100 cases of IDDM in the study range.

After we identified countries with data meeting the criteria mentioned above, Internet search engines, including Yahoo and Hotbot, were used to determine the status of military conscription in these countries. The name of the country, *military*, and *conscript* were used as key words for the Internet search. In the case of Belgium, we contacted the library of the military academy by e-mail to find out when the draft was ended.

Statistical Analyses

The mean incidence of IDDM in the control group was determined by a weighted numerical average, using the sum of all the cases of IDDM and the years of follow-up from all centers. The incidence of IDDM at any given sex and age group was published for each center. All centers except Sweden published the number of cases of IDDM for each sex and age group. For Sweden, the total number of cases for males and females was published for ages 15 to 35 and the number of patient year follow-up (number of patients × years followed) was published.

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Based on this information and the incidence of IDDM for each age and sex group, an estimate of the number of cases of IDDM was calculated. To be conservative with the Swedish data, we used a patient year follow-up size, 1 million, in each group that was in the minimum of the range we expected for each group.

Relative risks and other calculations were made using Epi 6 software (available at the Center for Disease Control's Web site). A 2×2 table was used, and the total number of cases of IDDM and the numerator for the control group and the US Navy were included. An uncorrected chi-square test was used, as well as Taylor series 95% confidence limits, and relative risk figures were rounded to the nearest tenth.

Results

We found published papers on the incidence of IDDM from the US Navy and several Western European countries. We did not find studies from several other Western European countries, Australia, New Zealand, or Canada, however. The incidence of IDDM for adults from 15 to 35 was available (Table 1) for Sweden,[7] Italy,[8,9] Belgium,[10] Spain,[11] and Norway.[12,13] These 5 countries had laws drafting men but not women. The incidence of IDDM in white men and women who had joined the US Navy was also published.[14] No other studies were found that met the entry criteria.

The data indicate that in the countries where men, but not women, are drafted, the incidence of IDDM is greater in men than women. In both men and women 20 or older the relative risk is 1.68 (1.53-1.84). By contrast, in US military personnel, the risk of IDDM is slightly lower in men than in women (relative risk 0.8; range 0.64-0.97). In Sweden, Italy, Belgium, Spain, and Norway, the relative risk of males and females for children up to 14 years old is about 1.1.[2]

The risk of IDDM is higher in US military men than in conscripted European men ages 20 to 35 (relative risk 1.6; 1.45-1.73), but the relative risk is even higher in US Navy women than in conscripted women (3.4; 2.7-4.26). The incidence of IDDM in young US military personnel (17 to 19 years) is initially on a par with the European populations and US civilians.[15] In male US Navy personnel, the incidence of IDDM increases gradually over comparable conscripts from European countries with time: relative risk rises from 1.3 (1.17-1.51) at ages 20 through 24 to 2.5 (2.01-3.03) at ages 30 through 34. A rise in the relative risk is also seen in US Navy women as compared to controls: 3.0 (2.26-4.07) at ages 20 through 24 to 5.6 (2.9-10.85) at ages 30 through 34. The calculated cumulative increased risk of IDDM in white US military women versus nonconscripted European women from age 20 through age 34 is 328 cases/100,000.

Discussion

These data are consistent with our previously published data[4-6] showing that groups which receive vaccines are at increased risk of diabetes. Our earlier data demonstrated an association between immunization with hepatitis B vaccine,[4] bacille Calmette-Guérin (BCG) vaccine,[4] and the hemophilus B vaccine[6] and increased risk of IDDM. The relative risks were 1.6, 1.7, and 1.25, respectively.

Our present study revealed that few articles have been published on the incidence of IDDM in adults. We were able to find only a single study on the incidence of IDDM in a military group in Europe or the United States. Adequate data exist on the incidence of IDDM in young adults in 5 European countries, but we were unable to find a single article that met our criteria and contained information on the incidence of IDDM in young civilians in the United States. One article estimating the incidence of IDDM in young adults in the United States, taken from data on cases occurring before 1970, did reveal incidence data similar to what is published in Europe.[16]

There are several findings in our analysis which support an association between vaccination and IDDM. In countries where men, but not women, are drafted and immunized by the military, the men have about 1.7 times (1.53-1.84) the risk of developing IDDM as the women. By contrast, in the US Navy, where men and women are both expected to receive military vaccines, the incidence of IDDM is less common in men (relative risk, 0.8; 0.64-0.97). Diabetes is more common in highly immunized US military men than in less-immunized conscripted European men (1.6; 1.45-1.73). However, the risk of IDDM is even more pronounced in US Navy women as compared to nonconscripted European women (3.4; 2.7-4.26). The difference in IDDM in US Navy men and conscripted men in Europe can be explained by the more extensive use of vaccines in the US military. For example, during the time studied, Sweden's military routinely gave the troops the diphtheria-tetanus vaccine but few others (H. Heijbel Infectious disease/vaccine safety expert, Swedish Public Health Department, oral communication, 1999). The United States, by contrast, typically gives military personnel many more vaccines.

The incidence of IDDM in the US Navy increases with age and years of exposure, further supporting an association between vaccination and IDDM. The incidence of IDDM declines with time in nonconscripted European women from 10.6 cases/100,000 in the 15 to 19 age group to 5.9/100,000 in the 30 to 34 age group (relative risk 0.56; 0.44-0.72. By contrast, in heavily immunized US Navy women, the incidence of IDDM increases from 12.6/100,000 in the 17 to 19 age group to 33.2/100,000 in the 30 to 34 age group (relative risk

TABLE 1
Incidence of Insulin-Dependent Diabetes Melitis in Europeans* and in White US Sailors

	Actual Number of Cases (Cases/100,000)							
	15 to 19 years old		20 to 24 years old		25 to 29 years old		30 to 34 years old	
	Men	Women	Men	Women	Men	Women	Men	Women
Sweden, 1983-1987	180 (18)	113 (11.3)	173 (17.3)	83 (8.3)	146 (14.6)	87 (8.7)	134 (13.4)	59 (5.9)
Belgium, 1989-1995	21 (11)	17 (9.2)	18 (7.9)	19 (8.6)	35 (13.4)	16 (6.4)	32 (12.2)	15 (6)
Italy								
Turin, 1984-1991	69 (10.1)	40 (6.1)	59 (8.0)	34 (4.9)	47 (7.0)	26 (4.0)		
Sardinia, 1989-1990	49 (31.8)	20 (13.5)	30 (18.9)	23 (14.9)	34 (25.3)	10 (7.5)		
Spain								
Catalonia, 1987-1990	138 (13.9)	83 (8.8)	119 (12.5)	66 (7.1)	100 (11.2)	51 (5.7)		
Norway, 1978-1982	157 (19.6)	117 (15.4)	124 (15.7)	100 (13.2)	165 (21.1)	121 (16.4)		
Total European	614 (16.1)	390 (10.6)	523 (13.5)	325 (8.7)	527 (14.4)	311 (8.5)	166 (13.2)	74 (5.9)
	17 to 19 years old							
US Navy	125 (12.5)	8 (12.6)	421 (18)	51 (26.2)	235 (24.1)	24 (29.8)	197 (33.2)	10 (33.2)

* Conscripted European men and nonconscripted European women

2.63; 1.04-6.69). A similar though less pronounced effect is seen in men. The incidence of IDDM in conscripted European men was fairly constant, from 13.5/100,000 in the 15 to 19 age group to 13.2/100,000 in the 30 to 34 age group (relative risk 0.97; 0.82-1.16). By contrast, the incidence of IDDM in US Navy men increases from 12.5/100,000 in the 17 to 19 age group to 32.4/100,000 in the 30 to 34 age group (relative risk 2.59; 2.07-3.24). In US Navy men, the incidence of IDDM increases gradually over comparable conscripts from European countries with time (relative risk at ages 20-24: 1.3, 1.17-1.51; at ages 30-34: 2.5, 2.01-3.03). A rise in the relative risk is also seen in US Navy women compared to controls, from 3.0 (2.26-4.07) at ages 20 to 24 to 5.6 (2.9-10.85) at ages 30 to 34. The rise in incidence for the women is about as large as that for the men but does not reach statistical significance because of the smaller number of women in the Navy.

The relative risk of IDDM between men and women in Belgium is particularly interesting. In those 25 or older, the relative risk between men and women is about 2.0, similar to many other countries. By contrast, the incidence of IDDM in men and women in the 20 to 24 age group is about the same. This could be explained by the fact that conscription was canceled in Belgium during the study period. A significant number of people in the 20 to 24 age group may not have served in the military or may have served a shortened term and thus had less exposure to vaccines. Older men had been conscripted into the military and had received vaccines, so this would explain the increased risk of IDDM in men compared to women. It is also possible that the incidence of IDDM was similar in men and women between 20 and 24 because of sampling error or random variation.

There are some limitations to this study. The number of cases in the civilian population may appear to be fewer than the number of military cases because better records are kept in the military. This is unlikely, however, to explain the 2-fold increase in IDDM in men versus women in a small country with a very good diabetes registry such as that in Sweden. Military personnel may be started on insulin sooner than civilians and thus may be more likely to be diagnosed with type 1 versus type 2 diabetes. In most countries with drafts, such as Sweden, most military recruits spend only a short time on active duty; most of their time is spent in the reserves, where they are treated primarily by civilian doctors.

The estimation of IDDM in the US Navy was made from hospitalization admissions. This system is not entirely accurate: the estimate may include cases of type II diabetes or have missed cases of IDDM that were treated without hospitalization. We do not believe, however, that, using this method, we have overestimated the incidence of IDDM. Our estimate appears to be accurate at least in the younger population: the incidence of IDDM in 17 to 19 year olds is actually less than in comparable groups in Europe and in the US civilian population,[15] suggesting that the Navy's data may actually underestimate the number of cases of IDDM. There are other potential causes of IDDM in military personnel, such as travel and exposure to infectious agents in foreign lands. While such factors may affect the outcome of a single study, it is very unlikely that they would result in all the associations found in many different studies.[4-6] Furthermore, the majority of conscripts in Europe probably do not travel abroad; thus, travel would not explain the difference between men and women in Europe.

Norway has the highest incidence of IDDM and the lowest male/female ratio of IDDM in any European country we studied. This can be explained by the criteria for estimating the incidence of IDDM. The authors[13] state that they may have included a number of cases of type II diabetes. However, even with this error, the incidence of IDDM in US Navy women is twice as high as women in Norway who are 20 or older.

The effect of environment, including temperature, geography, and diet, and of genetics have been attributed to the large variability in the difference in incidence of IDDM in children under 14 in different countries in Europe. These effects, with the exception of vaccines, appear to play much less of a role in older populations; the difference in incidence of IDDM in different European countries in women 25 to 29 years old is relative small, with a maximum difference of 12 cases/100,000 between countries. These factors thus do not explain the difference in IDDM between US Navy personnel and Europeans. Obesity can also not explain the findings, since military personnel must maintain body weight close to the ideal.

There are several mechanisms by which vaccines are expected to increase the risk of autoimmune diseases, including IDDM. Some vaccines contain molecules that immunologically cross react to the patient's antigens and are thus expected to be able to induce an immune response against the patient's tissue. For example, whole-cell pertussis vaccine[17] and BCG vaccine[18] contain heat shock proteins that cross react to pancreatic islet cell proteins and may induce IDDM. Vaccines also contain immune stimulants not associated with natural infections, and these substances can lead to aberrant immune responses. Macrophages are particularly stimulated by vaccine adjuvants, including aluminum[19] and complex polysaccharides,[20] similar to those found in certain capsular vaccines like pneumococcal and hemophilus vaccines. Insoluble polysaccharides,[20] like those found in

vaccines, are also more potent activators of macrophages than soluble polysaccharides, which may be more common in natural infections. Activated macrophages release alpha interferon, which has been repeatedly reported to cause IDDM in humans.[21-24]

Vaccines may also alter the ratio of T-helper 1 (TH1 and 2 lymphocytes. TH1 lymphocytes release gamma interferon, interleukin-2 (IL-2) and tumor necrosis factor. TH2 cells release IL-4, IL-5, IL-6, IL-10, IL-13. TH1 activity is associated with the destruction of islet cells; TH2 activity is not.[25,26]

It has been proposed that both the mumps and rubella[27-29] vaccines may infect the pancreatic islet cells and lead to the development of IDDM. Vaccines may also alter the risk of IDDM by increasing the expression of certain intrinsic viruses. Vaccines have been shown to cause the release of virus into the blood of individuals chronically infected with HIV.[30] It is possible that in individuals chronically infected with certain IDDM-causing viruses, vaccines could cause the release of these viruses into the blood, and the viruses could then infect islet cells.

Based on these data, the cumulative increased risk of IDDM associated with serving in the US Navy is 328 cases/100,000 (1:305) for active-duty personnel between the ages of 20 and 34. The data may underestimate the true risk of IDDM to a career person, however, since career personnel, who are likely to have a higher risk of IDDM because of their cumulative exposure to vaccines, are not differentiated from personnel who serve only a few years. We believe that the gradual increase in relative risk of IDDM with age shown in US Navy personnel compared to European controls is due to career personnel's cumulative exposure to vaccines. The increased risk of developing IDDM is likely to be extended until at least age 40 for a person serving in the military, and the risk of developing autoimmune diseases other than IDDM is likely to be as great as that for IDDM. The net result is that the risk of serious health-impairing reactions to vaccines in a person serving for 20 years in the US Navy may be significantly greater than 1:100, which may exceed the risk of being permanently disabled from battle wounds during a 20-year military career.

US servicemen and -women who are required to take certain vaccines are often concerned about their safety, particularly that of the anthrax vaccine and some others. Prior vaccine safety studies performed by the US military have used small populations, lacked controls, and lacked thorough follow-up,[1,2] including long-term follow-up.[3] By contrast, we studied data for IDDM in all Navy personnel. We have found that European populations serve as a good consistent control for the risk of IDDM in white US military personnel. These data seem to confirm the fears of US service men and women that the risk of adverse vaccine events may be quite high. Further follow-up is needed to determine if the risk of IDDM remains elevated after age 34 and if the incidence of other autoimmune diseases is increased as well.

The evidence suggests that vaccine-induced autoimmune diseases, including IDDM, are common conditions and are preventable. Immediate efforts are needed to ensure the safety of vaccines. In children, immunization starting in the first month of life should be considered as an option to decrease the risk of IDDM.[4,31] In adults, immunization should be withheld for individuals at high risk for any autoimmune disease. In adults with average risk for autoimmune disease, the number of doses of vaccine should be limited to optimize the risk-benefit ratio, as a dose response between vaccines and IDDM has been found with the hemophilus vaccine[6] and the measles-mumps-rubella vaccine.[3]

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